Chapter 7

Aortic prosthesis-patient mismatch and diminished exercise capacity in adult patients with congenital heart disease

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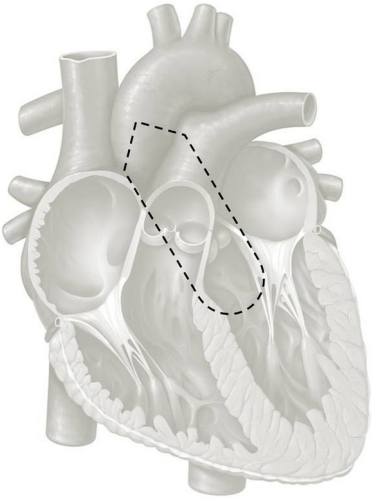

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Abstract

Background Grown-up patients with congenital heart disease (GUCH) with a history of aortic valve replacement (AVR) may outgrow their prosthesis later in life. However, the prevalence and clinical consequences of aortic prosthesis-patient mismatch (PPM) in GUCH-patients is presently unknown.

Methods From the national Dutch Congenital Corvitia (CONCOR) registry, we identified 207 GUCH-patients with an aortic valve prosthesis for this cross-sectional cohort study. Severe PPM was defined as an indexed effective orifice area $\leq$ 0.65 cm^2/m^2 and moderate PPM as an indexed orifice area $\leq$ 0.85 cm^2/m^2 using echocardiography. Exercise capacity was reported as percentage of predicted exercise capacity (PPEC).

Results Of the 207 patients, 68% was male, 71% had a mechanical prosthesis, and median age at inclusion was 45 years (interquartile range 35-53). The prevalence of PPM was 42%, comprising 23% severe PPM and 19% moderate PPM. Prevalence of PPM was higher in patients with mechanical prostheses ($p < 0.001$). PPEC was lower in patients with PPM (82% vs. 89%; $p = 0.030$). Using multivariable regression, PPM remained significantly associated with PPEC (ß = -11.05, $p = 0.039$), even when corrected for significant univariate parameters ($R^2 = 0.314$, $p = 0.001$).

Conclusions In this study we report a high prevalence (42%) of PPM in GUCH-patients with an aortic valve prosthesis and an independent association of PPM with diminished exercise capacity.

Introduction

Patients with (left-sided) Congenital Heart Disease (CHD) often need an aortic valve replacement (AVR) during childhood. These patients require life-long follow-up as they may encounter late prosthesis-related complications. One of these complications is prosthesis-patient mismatch (PPM), when the prosthesis essentially becomes too small for the patient's body size [1,2]. The prevalence and clinical consequences of PPM in Grown-Up patients with CHD (GUCH-patients) has not been investigated. The PROSTAVA study [3] was therefore set up to investigate the relationship between valve prosthesis-related characteristics and exercise capacity in GUCH-patients. Patients for the PROSTAVA study were selected from the CONCOR national registry [4] that aims to facilitate research on adult CHD patients by registering all GUCH-patients on a voluntary basis. In the PROSTAVA database we currently have almost 900 GUCH-patients with valve replacements in all 4 valvar positions, totalling data on approximately 1200 valve replacements.

In this manuscript, we focus on the PROSTAVA patients with aortic valve prostheses and report the prevalence of aortic valvar PPM and its effect on exercise capacity.

Methods

Patient population

In 2011, we selected all CONCOR-patients with an aortic valve prosthesis (n = 465) that were registered at one of the six participating PROSTAVA centres. Non-survivors (n = 36), prosthesis implantation in patients older than 50 years (n = 15), patients with a mental (n = 11) or physical disability (n = 21), no consent from treating cardiologist (n = 19), or patients who were enrolled into other studies (n = 16) were excluded. Thus a total of 347 individuals were approached to take part in the PROSTAVA-study [3]. Written informed consent was given by 207 patients (60%). Data concerning demography and medical history, including previous cardiac surgical interventions, were retrospectively collected by reviewing patient records. Prospective data comprised echocardiography, exercise testing, and laboratory blood tests. The ethical committees of the participating centers approved this study.

Echocardiography

Routine 2D, M-mode, and Doppler echocardiography (color, pulsed-wave (PW) and continuous-wave (CW Doppler)) was performed in all patients to assess ventricular and valvular dimensions and function. Left (systemic) ventricular (LV) ejection fraction (LVEF in %) was measured using Simpson's rule or by eyeballing when image quality was suboptimal. Further measurements included early septal and lateral diastolic annular velocity (E' in cm/sec), as well as tricuspid annular plane systolic excursion (TAPSE in mm). LV mass was calculated using the formula from Devereux et al. [5,6] Measurements on the aortic valve prosthesis comprised: maximum velocity (Vmax in m/sec), maximum gradient (Pmax in mmHg), mean gradient (Pmean in mmHg) and effective orifice area (EOA in cm^2). The continuity equation was used to calculate the aortic valve EOA [7]. The EOA was indexed to body surface area (BSA) to form iEOA in cm^2/m^2. BSA was calculated using the DuBois and DuBois formula (BSA = $0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425}$). PPM was defined as iEOA $\leq$ 0.85 cm^2/m^2, comprising moderate PPM (iEOA 0.85 to 0.65 cm^2/m^2) and severe PPM (iEOA $\leq$ 0.65 cm^2/m^2) [7]. Special attention was paid to possible evidence of other prosthesis related complications such as thromboembolism, pannus, valve degeneration, endocarditis, or paravalvular leakage.

Exercise capacity testing

Exercise capacity was tested using an upright bicycle ergometer or treadmill ergometer recording either the maximum oxygen uptake (VO_2peak in ml/min/kg) or the maximum workload (Wpeak in watts) depending on the resources of the participating hospital. All patients were continuously monitored using ECG, oxygen saturation and blood pressures. A predicted workload (Wpred) for ergometry was calculated using the equations based on Ascoop et al. [8] A predicted maximum oxygen uptake (VO_2pred) for VO_2peak testing was calculated using the Wasserman/Hansen equations as presented by Guazzi et al. [9] A short warm-up without load was followed by a stepwise increase of work load according to protocol based on age, sex, height and weight. We aimed for exercise duration of at least 6-8 minutes with symptoms prompting the end of the test. The achieved exercise level (Wpeak or VO_2peak) was divided by the predicted exercise level (Wpred or VO_2pred) to provide the percentage of predicted exercise capacity (PPEC). A PPEC $\leq$ 75% was considered to be poor exercise capacity [10]. To determine the chronotropic response, the

chronotropic index (proportional heart rate reserve) was calculated according to Lauer et al. [11] (chronotropic index = ((HRpeak - HRrest) / (HRpred - HRrest)) * 100). Patients were categorized as chronotropically incompetent if the chronotropic index was < 80% [12].

Analysis

Statistical analyses were performed using the statistical software package IBM SPSS Statistics version 20.0. Continuous data were tested for normality and are presented as mean ± standard deviation, as median with interquartile range (IQR), or as proportions for dichotomous variables. The $\chi 2$ test or Fisher's exact test was used to compare groups with categorical variables, Student's unpaired t-test for the analysis of normally distributed continuous variables or Mann-Whitney U-test for not normally distributed continuous variables. For the prosthetic valve size, the labelled size (in mm) as provided by the manufacturers was used. Variables associated with PPEC were investigated using univariable regression analyses. Based on literature [10,12] and our research questions, we included the following variables in our primary model: surgical parameters [mechanical prosthesis, prior intervention aortic valve apparatus, other valvular prostheses (mitral, pulmonary)], echocardiographic parameters [EOA (cm^2), iEOA (cm^2/m^2), PPM, LVEF (%), aortic valve Pmean (mmHg) LV mass (gr), TAPSE (mm), lateral and mean e' (cm/sec)], blood laboratory parameters [hemoglobin levels (mmol/L), log-transformed NT-proBNP (pg/mL)], exercise capacity parameters [resting blood pressure (mmHg), resting heart rate (bpm), and chronotropic incompetence], and lifestyle parameters [smoking]. To reduce the impact of positive skewness of NT-proBNP, it was log-transformed before it was entered into the regression model. Variables with a p-value of < 0.1 at univariable analysis were used in multivariable analysis and corrected for smoking habits and for BSA to equalize patients with different body sizes. The final multivariable model was constructed by backward deletion of the least significant characteristic and corrected for significant interactions. A two-sided p-value of < 0.05 was considered statistically significant.

Results

General

We included 207 adult CHD patients with their initial aortic valve prosthesis implanted between January 1973 and November 2011. Patient characteristics at cross-sectional analysis comprising demographics, medical history, echocardiographic parameters, and blood parameters are reported in table 1. General patient characteristics at the patient's first AVR are reported in table 2. The majority (75%) of our patients had left ventricular outflow tract obstruction (LVOTO) at birth. Ninety-two AVR-patients (44%) had a history of more than one aortic valve intervention (balloon or surgical valvulotomy, aortic valve repair or previous replacement). Seventy-one percent had a mechanical aortic prosthesis. Concomitant surgery at the last AVR comprised 37 PVRs in the setting of a Ross procedure (18%) and 6 other inventions on the right ventricular outflow tract or right atrioventricular valve (3%), 68 Bentall procedures or aortic root/ascendens replacements (33%), 20 interventions on left atrioventricular valve or left ventricular outflow tract (10%), 6 closures of intracardiac shunts (3%), and 1 coronary artery bypass grafting. In total, 98 patients (47%) had additional prostheses in the mitral or pulmonary position. Labelled aortic prosthetic sizes varied from size 19 mm to size 29 mm with size 23 mm being the most common. Almost all patients (99%) were in NYHA-class I or II at inclusion. The majority of patients were on medication including vitamin K-antagonists (76%), negative chronotropic medication (beta-blockers and calcium-channel blockers) (43%), renin-angiotensin system (RAS) inhibitors (38%), and/or diuretics (12%).

Echocardiography

Echocardiographic characteristics of the study population are presented in table 1. Seventy percent (n = 142) had a normal systemic ventricular ejection fraction (LVEF $\geq$ 55%) and 73% (n = 150) had a normal sub-pulmonary ventricular function (TAPSE $\geq$ 16 mm). TAPSE was negatively associated with prior surgical interventions of the right atrioventricular valve (n = 5, TAPSE 17mm (IQR 9-17) vs. 19mm (IQR 16-22); p = 0.051), but not by the presence of a pulmonary valve prosthesis (n = 88, TAPSE 19mm (IQR 16-21) vs. 19mm (IQR 16-23); p = 0.330).

Variable	Details	N(%) median(IQR)	N
Demographics at inclusion	Follow-up since first AVR (yrs)	13.7 (8.3-19.4)	207
	Age (years)	44.5 (35.3-53.0)	207
	BSA (m^2)	1.98 (1.84-2.14)	207
	NYHA-class (I-II)	156 (99%)	158
Medical history	First AVR	154 (74%)	207
	Second AVR	42 (21%)	207
	Third or fourth AVR	10 (5%)	207
	Mechanical prosthesis	147 (71%)	207
	Prosthesis labeled size (mm)	23.5 (23-25)	160
	Prior AVP/AVR/balloon dilation	92 (44%)	207
	Concomitant surgery	135 (65%)	207
	Other valvular prostheses in situ	98 (47%)	207
Echo-cardiography	LVEF (%)	60 (51-60)	202
	Indexed LV mass (g/m^2)	96 (76-116)	188
	TAPSE (mm)	19 (16-22)	185
	EOA (cm^2)	1.85 (1.33-2.63)	159
	iEOA (EOA/BSA in cm^2/m^2)	0.93 (0.68-1.33)	159
	PPM (iEOA $\leq$ 0.85 cm^2/m^2)	67 (42%)	159
	Pmean aortic valve (mmHg)	14.0 (5.9-20.6)	188
	Vmax aortic valve (m/sec)	2.5 (1.6-2.9)	194
	E' lateral (cm/sec)	13 (11-16)	81
	E' mean lateral and septal (cm/sec)	12 (10-13)	62
Blood laboratory	Hemoglobin levels (mmol/L)	9.1 (8.4-9.7)	181
	NT-proBNP (pg/mL)	126 (65-259)	156
	Renal function (eGFR) < 60 ($ml/min/1.73m^2$)	8 (4%)	183

Table 1 - Patient characteristics at cross-sectional analysis at inclusion in PROSTAVA (n = 207).
AVP: aortic valve plasty; AVR: aortic valve replacement; BSA: body surface area; E': early septal and lateral diastolic annular velocity; eGFR: estimated glomerular filtration rate; (i)EOA: (indexed) effective orifice area; LVEF: left ventricular ejection fraction; LV mass: left ventricular mass; NYHA: New York Heart Association; Pmean: mean pressure gradient; PPM: prosthesis-patient mismatch; TAPSE: tricuspid annular plane systolic excursion; Vmax: maximum velocity.

Variable	Details	N(%) or median(IQR)
Diagnosis	Congenital aortic valvar stenosis	155 (75%)
	Aortic subvalvar stenosis	7 (3%)
	Marfan syndrome	32 (16%)
	Other	13 (6%)
Demographics	Age (years)	28.1 (18.4-37.6)
	Sex (male)	139 (68%)
	BSA (m^2)	1.90 (1.70-2.07)
	Mechanical prosthesis	120 (58%)
	Subsequent redo-AVR	53 (26%)

Table 2 - Baseline characteristics at first AVR (n=207).
AVR: aortic valve replacement; BSA: body surface area; IQR: interquartile range.

Prosthesis-patient mismatch

Of all the patients with a valid measured EOA (n = 159), 67 patients (42%) had aortic valve PPM comprising 30 patients (19%) with moderate PPM (iEOA 0.85-0.65 cm^2/m^2) and 37 patients (23%) with severe PPM (iEOA $\leq$ 0.65 cm^2/m^2). The mean gradient across the aortic prosthesis was higher when PPM was present (Pmean 21.8 mmHg (IQR 15.5-28.1) vs. 10.1 (IQR 4.7-14.9); $p < 0.001$), as was the maximum velocity (Vmax 3.0 m/sec (IQR 2.7-3.5) vs. 2.2 (IQR 1.5-2.6); $p < 0.001$). The prevalence of PPM was higher in patients with a mechanical prosthesis (51% vs. 14%; $p < 0.001$) and in patients with a smaller (labelled size $\leq$ 22mm) prosthesis (87% vs. 38%; $p < 0.001$). Patients with severe PPM were younger at AVR compared to patients without PPM (median 27 years (IQR 16-39) vs. 34 (IQR 23-41); $p = 0.039$). GUCH-patients that were under 18 years old when they received their aortic valve prosthesis (n = 28) tended to develop PPM more often compared to those who received their prosthesis when already adult (57% vs. 39%; $p = 0.076$), this was especially true for the development of severe PPM (48% vs. 25%; $p = 0.025$). None of the patients with a Ross autograft had PPM.

Exercise capacity

In total, 158 patients (76%) completed an exercise capacity test (table 3) with 118 peak VO_2 tests (75%) and 40 ergometric tests (25%). The overall PPEC was median 85% (IQR 73-101%, mean 88%), with 49 patients (31%) scoring considerably poor on exercise capacity (PPEC $\leq$ 75%) of which 63% had a poor chronotropic response (chronotropic index < 80%). Overall, patients with chronotropic incompetence (n = 55, 35%) were on negative chronotropic medication more often compared to patients with a good chronotropic response during exercise (50% vs. 30%; p = 0.033). PPM was significantly associated with poorer PPEC (PPM 82% (IQR 66-100) vs. no PPM 89% (IQR 79-106); p = 0.030).

Variable	Details		N (%) or median (IQR)	N
VO_2peak	Rest	HR (bpm)	76 (66-84)	118
		RR systolic (mmHg)	125 (110-139)	97
	Peak	HR (bpm)	173 (155-182)	118
		RR systolic (mmHg)	170 (150-195)	97
		VO_2peak (ml/min/kg)	28.3 (23.1-35.3)	118
		PPEC (%)	84 (70-98)	118
		RQ	1.13 (1.07-1.18)	83
		Chronotropic index (%)	95 (77-102)	118
		Chronotropic incompetence	38 (32%)	118
Ergometry	Rest	HR (bpm)	74 (66-84)	40
		RR systolic (mmHg)	127 (119-150)	38
	Peak	HR (bpm)	158 (144-169)	40
		RR systolic (mmHg)	185 (160-206)	40
		Work (Watts)	168 (140-198)	40
	PPEC (%)	95 (80-110)	40	
		Chronotropic index (%)	86 (78-96)	40
		Chronotropic incompetence	17 (43%)	40

Table 3 - Exercise capacity (total n=158).
HR: heart rate; PPEC: percentage of predicted exercise capacity (VO_2peak or ergometry); RQ: respiratory quotient; RR: blood pressure; VO_2: oxygen uptake.

Predictors of exercise capacity

Univariable parameters associated with PPEC ($p < 0.1$) included the presence of other valvular prostheses, PPM, LVEF, TAPSE, aortic valve Pmean, blood haemoglobin levels, log-transformed NT-proBNP, resting systolic blood pressure at exercise testing, and evidence of chronotropic incompetence (table 4 on opposite page). In the multivariable model, PPM remained significantly associated with a poorer exercise capacity, even when corrected for TAPSE, log-transformed NT-proBNP and chronotropic incompetence ($R^2 = 0.314$, $F = 4.270$; $p = 0.001$) as shown in table 5 below.

Method	Variable	B	95% CI (B)	t	p-value
Echo-cardiographic	PPM	-11.05	-21.52 to -0.577	-2.114	0.039
	TAPSE (mm)	1.251	0.019 to 2.482	2.035	0.047
Blood tests	Log NT-proBNP (pg/mL)	-13.07	-23.92 to -2.207	-2.410	0.019
Exercise testing	Chronotropic incompetence (index < 80%)	-12.27	-23.24 to -1.310	-2.243	0.029

Table 5 - Multivariate parameters associated with percentage of predicted exercise capacity (PPEC).
B: unstandardized coefficient; CI: confidence interval; log: logarithmic-transformed; PPEC: percentage of predicted exercise capacity; PPM: prosthesis-patient mismatch; t: ratio of B to standard error of B; TAPSE: tricuspid annular plane systolic excursion.

Method	Variable	B	95% CI (B)	t	p-value
Patient	BSA (m^2)	-6.827	-21.94 to 8.289	-0.892	0.374
Surgical	Mechanical prosthesis	-5.380	-12.63 to 1.868	-1.466	0.145
	Prior intervention aortic valve apparatus	-3.913	-10.73 to 2.902	-1.134	0.258
	Other valve prostheses (mitral or pulmonary)	-6.910	-13.65 to -0.173	-2.026	0.044
Echo-	EOA (cm^2)	0.957	-2.924 to 4.838	0.488	0.626
cardiographic	iEOA (cm^2/m^2)	3.372	-4.793 to 11.54	0.818	0.415
	PPM (iEOA $\leq$ 0.85 cm^2/m^2)	-8.285	-16.50 to -0.074	-1.998	0.048
	Pmean aortic prosthesis (mmHg)	-0.325	-6.82 to 0.031	-1.803	0.073
	LVEF (%)	0.560	0.017 to 1.103	2.038	0.043
	Indexed LV mass (g/m^2)	0.040	-0.087 to 0.166	0.621	0.536
	TAPSE (mm)	1.104	0.261 to 1.947	2.588	0.011
	E' lateral (cm/sec)	0.648	-0.902 to 2.197	0.835	0.407
	E' mean of lateral and septal (cm/sec)	1.243	-0.833 to 3.319	1.203	0.235
Blood tests	Hemoglobin levels (mmol/L)	3.289	-0.604 to 7.183	1.671	0.097
	Log NT-proBNP (pg/mL)	-7.563	-15.73 to 0.601	-1.834	0.069
Exercise testing	Resting systolic blood pressure (mmHg)	0.194	-0.003 to 0.391	1.945	0.054
	Resting heart rate (bpm)	-0.075	-0.309 to 0.160	-0.630	0.530
	Chronotropic incompetence (index < 80%)	-19.28	-26.34 to 12.21	-4.854	< 0.001
Lifestyle factors	Smoking	-9.438	-21.86 to 2.986	-1.504	0.135

Table 4 - Univariable parameters associated with PPEC.
B: unstandardized coefficient; BMI: body mass index; BSA: body surface area; CI: confidence interval; E': early septal and lateral diastolic annular velocity; (i)EOA: (indexed) effective orifice area; log: logarithmic-transformed; LVEF: left ventricular ejection fraction; LV mass: left ventricular mass; Pmean: mean pressure gradient; PPEC: percentage of predicted exercise capacity; PPM: prosthesis-patient mismatch; t: ratio of B to standard error of B; TAPSE: tricuspid annular plane systolic excursion.

Discussion

In this young GUCH-population (median age 45 years), the prevalence of aortic valve PPM was 42% of which more than half were classified as severe PPM. Patients with PPM had a significantly lower exercise capacity. To our knowledge, this is the first report on PPM and exercise capacity in GUCH-patients.

PPM was first described in 1978 by Rahimtoola [2] and he defined it as such: 'Mismatch can be considered to be present when the effective prosthetic valve area, after insertion into the patient, is less than that of a normal human valve', and stated that PPM is basically an obstruction to ventricular outflow and/or inflow. The prevalence (42%) of overall PPM in our population was comparable with the prevalence (44%) in studies on elderly patients, but the prevalence of severe aortic valve PPM in our GUCH-population was more than twice as high (23%) compared to reports in non-GUCH patients (10%) [13,14]. Somatic growth is likely the main reason for this difference in prevalence, as nearly half of the GUCH-patients that received an aortic valve prosthesis as a child developed severe PPM in our study, compared to only 25% in those who had the AVR as an adult.

Exercise capacity in GUCH-patients

The mean achieved exercise capacity in this study was 88% of the predicted value, which is slightly higher than other reports on GUCH-patients, but lower than healthy controls [15-17]. Reasons for diminished exercise capacity in patients with CHD may include pulmonary, vascular, metabolic or cardiac impairments [18]. We focused on the latter and the major finding in this study is that aortic PPM is associated with decreased exercise capacity in GUCH-patients, even when corrected for significant univariate parameters. This has not been reported before. Only recently, Bleiziffer et al. [10] reported a reduced PPEC in elderly patients with aortic PPM (ß = -0.079, p = 0.007). They stated that poorer PPEC in patients with PPM is possibly caused by an increased hemodynamic burden because of higher gradients as also seen in native aortic valve stenosis [10]. These higher transprosthetic gradients limit the necessary increase of cardiac output during exercise [19]. In our study, we observed a significantly lower PPEC in patients with PPM (82% vs. 89%) with higher gradients and velocities across the aortic prostheses. Diller et al. [17] found that GUCH-patients with a poor exercise capacity are at a higher risk of hospitalization or death (HR 2.9; 95% CI 2.2-7.4; $p < 0.001$). We report

that as much as 31% of patients had a poor exercise capacity and PPM was one of the determinants of diminished exercise capacity in our study. Patients with diminished PPEC and/or PPM may be at increased risk of complications including mortality, since both poor exercise capacity as well as PPM have been related with decreased survival [13,17].

Other predictors of exercise capacity

In our regression models, chronotropic incompetence, log-transformed NT-proBNP, and TAPSE were significantly related to exercise capacity in the multivariable model. Chronotropic incompetence was observed in 35% of our patients and is often the result of abnormal cardiac rhythm or negative chronotropic medication such as beta-blockade [17]. Though it is obvious that right ventricular function can be important for exercise capacity, it is less clear why the TAPSE would be diminished in a GUCH-population with mainly aortic valve prostheses. A history of right-sided cardiac surgical interventions, such as right atrioventricular valve repair or pulmonary valve replacement, is seen in almost half of this GUCH-population but might not sufficiently explain the difference in TAPSE. NT-proBNP levels have been associated with diminished exercise capacity before and is seen as an identifier of functional impairment [20].

Avoidance of PPM

Identified risk factors in the literature for aortic PPM in non-GUCH patients include female sex (smaller aortic root compared to body size)[21-25], hypertension (associated with left ventricular hypertrophy and calcification of aortic valve) [22, 25], older age (calcification due to an inflammatory process facilitated by atherosclerotic risk factors) [23,25-29], and large BSA (intrinsic to the equation of iEOA) [26,30]. In GUCH-patients who received an aortic prosthesis at a young age, somatic growth leading to an increase in BSA is likely an important risk factor for PPM. In our study the implantation of a mechanical and/or a small ($\leq$ 22mm) aortic prosthesis at a younger age increased the prevalence of PPM. By implanting a prosthesis that will grow with the patient (e.g. an autologous graft) or by implanting a prosthesis that is large enough to accommodate the patient's hemodynamic needs for a longer period of time, PPM may be postponed or avoided. Whenever possible, valve repair is the preferred strategy to prevent PPM in the growing child. But when repair is deemed impossible, the timing of the valve

replacement is crucial and postponement of intervention aimed at allowing the child to grow, has to be weighed carefully against the possible risk of sudden death or development of irreversible ventricular dysfunction. If postponement is not an option, the surgeon should preferably try to implant a prosthesis with the largest possible EOA for the patient's annulus size, or even decide to increase the annulus size to fit a larger prosthesis. It must be noted however, that EOAs of different valve models vary greatly, despite the same labelled size [13].

Limitations

To obtain acceptable numbers, this study covers a long period of time in which surgical techniques and peri-operative care have changed. A multicenter study was used to approximate the functional outcomes of a GUCH-population with aortic valves, even though protocols differ slightly between centres.

Conclusions

In this study we report a high prevalence of PPM in GUCH-patients with an aortic valve prosthesis and an independent association of PPM with diminished exercise capacity.

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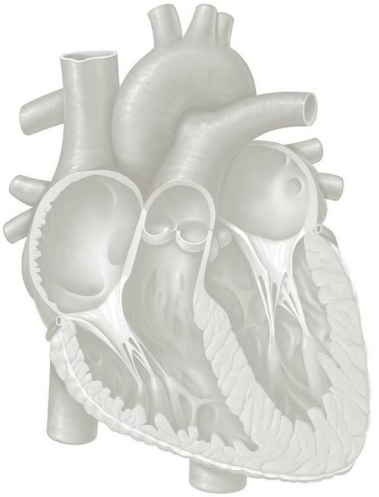
Summary



"An honest tale speeds best, being plainly told."

William Shakespeare (1564-1616)
King Richard III, Act IV, Scene IV

In this thesis the long-term follow-up results of patients with cardiovascular prostheses used to palliate or repair congenital heart defects (CHD) are presented. The type of material, the size of the prosthesis, and the timing of the intervention can have a large impact upon the long-term development and survival of the child. Due to incredible progress within the care delivered to these CHD-patients, more and more patients survive into adulthood and become Grown-Ups with CHD (GUCH-patients) also known as Adults with CHD (ACHD). This has presented caretakers with a new group of patients that carry an interesting range of prosthetic materials with them of which the long-term effects are largely unknown.

Chapter 1

The effect of additional pulmonary blood flow on timing of the total cavopulmonary connection.

The staged Fontan procedure is used to palliate functionally univentricular hearts. The effect of combining a bidirectional cavopulmonary shunt with additional pulmonary blood flow in these patients remains a controversial subject [1-4]. Advantages of additional pulmonary blood flow may include higher oxygen saturations, increased pulmonary artery growth, and implantation of a larger extracardiac conduit at completion of the total cavopulmonary connection. However, disadvantages may include elevated central venous pressure in the upper body, increased ventricular volume load, a negative effect on final Fontan candidacy, and increased interval morbidity [5-8]. This retrospective study included all 82 patients with a unilateral or bilateral bidirectional cavopulmonary shunt at our institution between April 1990 and July 2010. Patients with hypoplastic left heart syndrome were excluded. Two groups based on the presence (n = 57) or absence (n = 25) of additional pulmonary blood flow were compared. We found that patients with a bidirectional cavopulmonary shunt and additional pulmonary blood flow have a longer interval before the total cavopulmonary connection is prompted, without evident untoward effects. Postponement of the total cavopulmonary connection may give the child more time to grow so a larger extracardiac conduit may be implanted at completion of the Fontan circulation and possibly aid in avoiding prosthesis-patient mismatch (PPM). Because all venous flow from the lower body returns to the heart via the extracardiac conduit in a Fontan circulation, PPM of this conduit can result in ascites, peripheral edema, and decreased cardiac output and thus limited exercise capacity [9,10]. Eventually the conduit will

need to be replaced by a larger one, but the effects on the patient's body may be irreversible and moreover, reoperation may not always be possible. We therefore advocate the preservation of a calibrated amount of additional pulmonary blood flow to allow the child to grow and potentially reduce the risk of PPM following the total cavopulmonary connection.

Chapter 2

Quantification of ventricular volume load in the context of a bidirectional cavopulmonary shunt: A theoretical treatise.

Besides possible avoidance of PPM when preserving an additional source of pulmonary blood flow, the pulmonary arteries also have more time to grow which may prove vital for a successful Fontan circulation. However, too much additional pulmonary blood flow can have a deleterious effect on univentricular functioning and development by adding disproportionally to the ventricular volume load [11,12]. To minimize the risk of ventricular overloading during the staged Fontan, we devised a theoretical framework to facilitate a more precise calibration of the amount of additional pulmonary blood flow when creating a bidirectional cavopulmonary shunt. Using the Fick principle and the oxygen saturations of intraoperative blood samples from specific blood compartments, the proportions of blood volumes in those different compartments can be estimated. By estimating these volumes as a proportion of flow in the inferior vena cava during two different flow scenarios, one with and one without an additional source of pulmonary blood flow, one can quantify the difference and thus the additional volume load on the single functional ventricle. This may provide caretakers with the means to take patient-focused decisions intraoperatively so the possible advantages of a source of additional pulmonary blood flow can be fully exploited without carelessly risking significant ventricular overloading.

Chapter 3

Prosthetic valves in adult patients with congenital heart disease: Rationale and design of the Dutch PROSTAVA study.

Data on long-term complications in GUCH-patients with valvular disease and prosthetic heart valves are scarce. To shed some light on the effects of valvular prostheses on GUCH-patients, we devised the multi-centre cross-sectional PROSTAVA study of

which the design is presented in chapter 3. Its primary objective was to investigate the relationship between prosthetic valve characteristics (type, size and location) and exercise capacity as well as quality of life in GUCH-patients. The secondary objective was to investigate the prevalence and predictors of prosthesis-related complications including PPM.

For the PROSTAVA study, we collected retrospective surgical and follow-up data (including short- and long-term valve-related complications) on 829 patients from the national CONCOR registry [13] that proved eligible for the PROSTAVA study, totaling data on 1207 valve replacements in all 4 valvular positions. After excluding patients that did not meet the inclusion criteria for the cross-sectional analysis we approached 632 patients of which 406 gave their informed consent (64%). The cross-sectional investigation involved echocardiography, ECG, exercise testing (VO_2max or ergometry), quality of life questionnaires (SF-36), 24-hour ECG, laboratory blood tests and an MRI scan. An additional telephonic questionnaire was conducted to acquire data on use of medication and impact of oral anticoagulation and audible valve clicks on quality of life. During the PROSTAVA study, we lost 18 patients because they passed away, withdrew or became pregnant. Thus, a total of 388 patients had been included in the PROSTAVA study at the end of the project for cross-sectional investigation.

It is the first study that focuses on functional outcome in GUCH-patients and the results may influence the way we care for patients with CHD.

Chapter 4

Long-term tricuspid valve prosthesis-related complications in congenital heart disease.

Tricuspid valvular dysfunction is common in elderly patients, but only a small proportion is caused by CHD, be it structural (e.g. Morbus Ebstein) or functional (e.g. secondary to dilation of the right ventricle and/or pulmonary hypertension) [14]. Sometimes a replacement of a dysfunctional tricuspid valve in young patients is necessary, but the long-term results are unclear. From the PROSTAVA database we thus identified 20 GUCH-patients with a biological or mechanical tricuspid valve prosthesis implanted between 1977 and 2012 (total of 31 prostheses) at a mean age of 30 ± 16 years. During a mean follow-up of 14 years, 50% needed a re-replacement because of valve-related complications including PPM. This prosthesis-related complication rate is higher compared with studies in patients with acquired valve disease reporting

long-term complication rates of 10-35% during a shorter mean follow-up time (6-9 years) [14-18]. The higher complication rate in our population can be explained by the longer follow-up time, but also by the young age of our population. The management of anticoagulation in young patients is more challenging as these patients may be less compliant because of life phase and lifestyle. In addition, mechanical valves in young (fertile) patients have an increased risk of valve thrombosis during pregnancy despite strict compliance with oral or heparin anticoagulation [19]. In bioprostheses, young age increases the risk of early deterioration [20,21]. We found that even though the prosthesis-related complication rate was higher in GUCH-patients, the indications for reoperation in the PROSTAVA study are similar to other studies on prosthetic tricuspid valves: valve thrombosis in mechanical valvular prostheses and structural valve deterioration in bioprosthetic valves [14,15,22-24]. Our data further suggests that PPM has a significant negative effect on the duration of the event-free survival post-implantation. We emphasize that the choice of prosthesis with regard to size and design should remain individualized and that caretakers need to remain vigilant of PPM.

Chapter 5

Long-term mitral valve prosthesis-related complications in congenital heart disease.

A dysfunctional mitral valve in children with CHD is preferably repaired, but sometimes replacement of the native mitral valve (MVR) is inescapable. However, children with a mitral valve prosthesis are vulnerable to valve-related complications, such as accelerated degeneration of bioprostheses or PPM due to somatic growth, which result in high reoperation rates (13-37%) [25-31]. Possible variables associated with replacement of the prosthetic valve are young age [25] and smaller prosthesis [25,28] at first mitral valve replacement, and multiple left-sided obstructive lesions at birth [32]. Whether these predictors also apply to older patients with CHD is unknown. In chapter 4 we therefore report the long-term prosthesis-related complications in 91 GUCH-patients with a median age of 29 years (interquartile range 13-44) with a mitral valve prosthesis implanted between 1978 and 2010. During a median follow-up of 12 years almost 50% of GUCH-patients encountered prosthesis-related complications that necessitated a replacement of the dysfunctional prosthesis in almost one-third of our patients. Most (75%) of the complications arose at adult age. The main reason for redo MVR was obstruction (PPM or pannus), followed by biological valve deterioration,

endocarditis and paravalvular leakage. The presence of left-sided obstructive lesions at birth, small indexed prosthesis size at implantation and MVR before the year 2000 prove independent variables associated with prosthesis-related complications following the MVR regardless of the reason for the actual MVR. Patients that had the MVR before the year 2000 were younger which increases the risk of reoperation on the long-term. Furthermore, patients with left-sided obstructive heart lesions (mitral valve stenosis, (sub)valvular aortic valve stenosis, or aortic coarctation) received smaller sized prostheses than patients without left-sided obstructive lesions. We therefore hypothesize that the higher incidence of complications in patients with left-sided obstructive lesions is explained by smaller intra-cardiac dimensions relative to body size. As a consequence, their smaller prosthesis size could lead to an increased risk of PPM, which, in our study, occurred 4 times as often in patients with left obstructive lesions. This thought is strengthened by the fact that indexed prosthesis size (iGOA) remains significantly associated with valve-related complications. However, there may be other risk factors specific to patients with left-obstructive lesions that are of importance for cardiac prognosis that we have not yet uncovered.

Chapter 6

Pulmonary valve replacement: Long-term outcome of mechanical valve prostheses.

Many patients with right-sided CHD need replacement of a dysfunctional pulmonary valve (PVR) [33,34]. Bioprostheses are often preferred as they pose a low thrombogenic risk in the pulmonary position and because their deterioration rate is lower than in left-sided prostheses. Despite their low deterioration rate, they will eventually need to be replaced due to prosthetic dysfunction in the long run. Alternatively mechanical valve prostheses are more durable, but these require strict anticoagulation. Several studies with a relative short follow-up have shown that mechanical prostheses may be used, but only in combination with strict anticoagulation therapy [35,36]. Whether mechanical pulmonary valve prostheses in CHD-patients perform as well over a longer period of time is unknown.

In chapter 6 we therefore report the long-term follow-up of 66 CHD-patients with mechanical valve prostheses in the pulmonary position. Prostheses were implanted between 1987 and 2013 at a mean age of 35 ± 13 years. The main underlying diagnosis was Tetralogy of Fallot. Overall, 12 patients (18%) died and 8 patients (12%)

suffered prosthesis-related complications during a mean follow-up of 6 ± 5 years. Valve thrombosis was the main prosthesis-related complication (9%) resulting in a mechanical valve thrombosis incidence of 1.5% patients/year. Six (9%) redo PVRs were needed which was comparable with the redo rates seen in homografts [37,38]. The relatively high mortality rate is possibly explained by negative selection bias as patients with more severe disease were more likely to receive a mechanical prosthesis than a bioprosthesis to avoid future re-PVR.

Long-term success of PVR using mechanical valve prostheses is limited because of valve thrombosis (often in the setting of pregnancy or incompliance with anticoagulation therapy) and bleeding complications. Performance of mechanical valve prostheses may improve when valve thrombosis is prevented by patient selection, avoiding mechanical valves in patients at increased risk of valve thrombosis, and by strict compliance to anticoagulation therapy.

Chapter 7

Aortic prosthesis-patient mismatch and diminished exercise capacity in adult patients with congenital heart disease.

Patients with left-sided CHD sometimes need an aortic valve replacement (AVR) during childhood. Because of the risk of late prosthesis-related complications, they require a life-long follow-up. One of these complications is PPM negatively facilitated by the child growing up, but the prevalence and clinical consequences of aortic PPM in GUCH-patients are unknown.

From the PROSTAVA database we identified 207 GUCH-patients with an aortic valve prosthesis implanted between 1973 and 2011 at a median age of 45 years (interquartile range 35-53). Seventy-one percent of patients received a mechanical prosthesis. Using echocardiography, we established that 19% of GUCH-patients with an aortic valve prosthesis has moderate PPM and an additional 23% has severe PPM. The prevalence of (severe) PPM is higher in patients with a mechanical prosthesis and in patients that received their aortic prosthesis before they were 18 years old. Compared with literature on patients with acquired aortic valve disease and AVRs, the prevalence of severe aortic valvular PPM is twice as high in GUCH-patients [39,40]. The negative clinical impact of aortic PPM in GUCH-patients on exercise capacity is significant. Furthermore, PPM remains significantly associated with a poorer exercise capacity even when corrected for TAPSE, log-transformed NT-proBNP and chronotropic incompetence.

We report that PPM is a prevalent problem in GUCH-patients with aortic valvular prostheses and needs to be acknowledged and if possible avoided as it has a negative upon the functional capacity of the patient.

Conclusion

Patients with CHD and cardiovascular prostheses differ in many respects from patients with acquired valve disease, but scientific evidence about the implications of these differences is scarce. In this thesis we report the long-term effects of the implantation of cardiovascular prostheses in patients with CHD and to relate their characteristics to functional outcome in a unique large-scale GUCH-patient cohort. Our results may influence the way we assess and manage adults with CHD and may influence the choice of valve prosthesis, the follow-up, the indication for more extensive surgery (e.g. annulus enlargement) and the indication for reoperation in patients with prosthesis-patient mismatch.

Future perspectives

GUCH-patients represent a new patient population with many unknown factors. Research into GUCH-patients with cardiovascular prostheses will therefore continue and often focus on measuring basic cardiovascular dimensions and functional performance that differ from 'healthy' patients. However, because of all the known complications related to cardiovascular prostheses, we may need to move from counting complications to designing new prostheses with superior performance. The use of stentless bioprostheses has already proven a small step forward, but perhaps the future is in the development of autografts grown from the patient's own cells. These tissue-engineered heart valves are similar to the native valve structure and may prove capable of growth, remodeling and repair [41]. Potentially, umbilical cord cells could be harvested from an embryo with CHD and engineered into a fully operational valve or conduit that can be implanted as soon as that child is born. Even though the exploration of a more sustainable cardiovascular prosthesis that is analogous to the native heart is still in the animal testing phase [42], the future looks promising.

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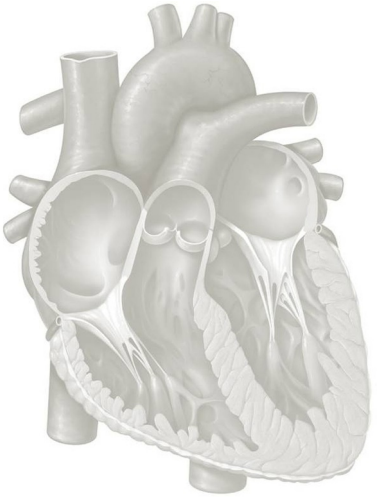
Nederlandse samenvatting

Summary in Dutch



"Repetitio mater scientiae est"

In dit proefschrift staan de lange termijn gevolgen gepresenteerd van het gebruik van cardiovasculaire prothesen om vele aangeboren hartafwijkingen (AHA) te pallieren of te repareren. De keuze van het prothesemateriaal, de prothesemaat en het moment van opereren kunnen een enorme impact hebben op de ontwikkeling en overleving van het kind. Wegens enorme vorderingen binnen de zorg worden steeds meer jonge patiënten met AHA volwassen. Deze nieuwe patëntenpopulatie draagt een breed scala aan prothesen met zich mee waarvan we de lange termijn gevolgen veelal niet kennen.

Hoofdstuk 1

The effect of additional pulmonary blood flow on timing of the total cavopulmonary connection.

De Fontan procedure bestaat uit een reeks van operaties met als doel het pallieren van functioneel univentriculaire harten. Tijdens de een-na-laatste operatie in deze Fontan reeks creëert de chirurg de bidirectionele cavopulmonale shunt waarbij bloed vanuit het bovenste deel van het lichaam direct naar de longen stroomt. Hiernaast kan men een extra bron aan bloed naar de longen (longflow) behouden via bijvoorbeeld een aortopulmonale shunt, maar daar is nog discussie over [1-4]. Mogelijke voordelen van een hogere longflow zijn hogere zuurstofsaturaties in het bloed, betere groei van de longslagaderen en uiteindelijk de mogelijkheid om een grotere vaatprothese te implanteren bij de laatste Fontan operatie: de totale cavopulmonale connectie. Mogelijke nadelen zijn een verhoogde centraal veneuze druk in de bovenste lichaamshelft, verhoogde volumebelasting van de enige functionele ventrikel, lagere succeskans bij de laatste Fontan operatie en hogere morbiditeit tussen de Fontan stappen door [5-8]. In deze retrospectieve studie beschrijven wij alle 82 patiënten met een unilaterale of bilaterale bidirectionele cavopulmonale shunt die tussen april 1990 en juli 2010 zijn geopereerd in ons ziekenhuis. Patiënten met een hypoplastisch linkerhartsyndroom werden geexcludeerd. De totale patiëntenpopulatie werd gesplitst in twee groepen: een groep met (n = 57) en een groep zonder (n = 25) additionele longflow naast de bidirectionele cavopulmonale shunt. Onze studie laat zien dat patiënten met additionele longflow langer kunnen wachten totdat de totale cavopulmonale connectie noodzakelijk was, zonder dat er duidelijke nadelige effecten zichtbaar waren. Door de totale cavopulmonale connectie uit te stellen heeft het kind mogelijk meer tijd om te groeien zodat er een grotere extracardiale vaatprothese geimplanteerd kan worden bij de totale cavopulmonale connectie. Denkbaar is dat

deze grotere buis de kans op prothese-patiënt mismatch (PPM) in een opgroeiend kind kleiner maakt. Omdat al het veneuze bloed vanuit de onderste lichaamshelft via deze vaatprothese rechtstreeks naar de longen moet stromen kan PPM van deze vaatprothese resulteren in ascitis, perifeer oedeem, verminderd hart-minuut-volume en derhalve een verminderd inspanningsvermogen [9,10]. Uiteindelijk zal in het geval van PPM deze vaatprothese vervangen moeten worden door een groter exemplaar, maar de negatieve effecten van PPM op de rest van het lichaam kunnen reeds onomkeerbaar zijn en bovendien is heroperatie niet altijd mogelijk. Wij pleiten daarom voor het behoud van een beperkte additionele longflow om het kind de tijd te geven om te groeien en daardoor mogelijk het risico op PPM na de totale cavopulmonale connectie te reduceren.

Hoofdstuk 2

Quantification of ventricular volume load in the context of a bidirectional cavopulmonary shunt: A theoretical treatise.

Door een extra bron van longflow te behouden bij patiënten met een functioneel univentriculair hart wordt mogelijk de kans op PPM verlaagd en krijgen bovendien de longarterieën meer tijd om te ontwikkelen. Dit laatste is essentieel voor een succesvolle Fontan circulatie. Echter als er te veel longflow is in het stadium vóór de totale cavopulmonale connectie raakt de enige functionerende ventrikel overbelast en verstoort dit de ontwikkeling van het reeds aangedane hart [11,12]. Om het risico van overbelasting te minimaliseren hebben wij een theoretisch rekenmodel ontwikkeld om de hoeveelheid longflow te calibreren tijdens het aanleggen van de bidirectionele cavopulmonale shunt. Met behulp van het Fick principe en intraoperatief gemeten zuurstofsaturaties van bloedmonsters uit verschillende compartimenten in en rondom het hart kunnen de volumeverhoudingen van die compartimenten geschat worden. Door alle volumes als proportie van de hoeveelheid bloedstroom in de vena cava inferior te zien kunnen verschillende berekeningen gedaan worden. In dit hoofdstuk berekenen we de verschillende volumes gedurende twee scenarios: één met additionele longflow en één zonder additionele longflow. Het verschil tussen deze twee scenarios geeft een schatting van de extra volumebelasting op de enige ventrikel. Dit model kan het intraoperatieve beslissingsproces meer patiëntgericht maken zodat de mogelijke voordelen van een extra bron aan bloedstroom naar de longen optimaal benut kunnen worden zonder significante ventrikel overbelasting te riskeren.

Hoofdstuk 3

Prosthetic valves in adult patients with congenital heart disease: Rationale and design of the Dutch PROSTAVA study.

Lange termijn gegevens over de gevolgen van een hartklepprothese in volwassen patiënten met een AHA zijn schaars. Om daar verandering in te brengen hebben we de multicenter cross-sectionele PROSTAVA studie opgezet welke beschreven staat in dit hoofdstuk. Het primaire doel was het onderzoeken van de relatie tussen de eigenschappen van de hartklepprothese (soort, maat en positie) en inspanningsvermogen en kwaliteit van leven in volwassen AHA patiënten. Het tweede doel was het in kaart brengen van de prevalentie en voorspellers van prothese-gerelateerde complicaties zoals PPM. Retrospectief hebben we de chirurgische en follow-up gegevens verzameld (inclusief korte en lange termijn klep-gerelateerde complicaties) van patiënten die geregistreerd staan in het Nederlandse CONCOR-register [13] en die voldeden aan de criteria voor de PROSTAVA studie. In totaal hebben we in de PROSTAVA studie gegevens van 829 patiënten met 1207 hartklepprothesen op verschillende posities in het hart. Na de exclusie van patiënten die niet voldeden aan de criteria voor de cross-sectionele analyse hebben we 632 volwassen patiënten met een AHA en een klepprothese benaderd waarvan 406 toestemming hebben gegeven (64%). Het cross-sectionele gedeelte van deze studie bestond uit een echocardiogram, een ECG, een inspanningstest (VO_2max of ergometrie), een kwaliteit-van-leven vragenlijst (SF-36), een 24-uurs holteronderzoek, bloedonderzoek en een MRI-scan. Een extra vragenlijst werd telefonisch afgenomen om gegevens te verkrijgen over medicijngebruik en de impact van orale anticoagulantia en klepgeluiden op de kwaliteit van leven. Gedurende de looptijd van de PROSTAVA studie zijn 18 patiënten alsnog geexcludeerd omdat zij waren overleden, zij zich terugtrokken of omdat zij zwanger raakten. In totaal waren aan het eind van de PROSTAVA studie dus 388 patiënten geincludeerd voor cross-sectioneel onderzoek.
Deze studie is de eerste die zich richt op de functionele uitkomsten in volwassen AHA-patiënten met een hartklepprothese. De resultaten veranderen mogelijk de manier waarop wij voor deze patiënten zorgen.

Hoofdstuk 4

Long-term tricuspid valve prosthesis-related complications in congenital heart disease.

Tricuspidalisklepdisfunctie komt vaak voor bij oudere patiënten maar is zeldzaam bij jonge patiënten met AHA. Bij deze patiënten kunnen structurele afwijkingen (bijv. Morbus Ebstein) of functionele afwijkingen (bijv. secundair door dilatatie van de rechter ventrikel en/of pulmonale hypertensie) zorgen voor een slecht functionerende tricuspidalisklep [14]. Soms is het noodzakelijk de afwijkende tricuspidalisklep te vervangen, maar er is nog geen duidelijkheid over de lange termijn gevolgen. In de PROSTAVA database hebben wij 20 volwassen AHA-patiënten met een biologische of mechanische tricuspidalisklepprothese die tussen 1977 en 2012 geimplanteerd is. In totaal waren er 31 klepprothesen geimplanteerd waarbij de gemiddelde leeftijd 30 ± 16 jaar was bij de implantatie van de eerste tricuspidaalklep. Gedurende een gemiddelde follow-up duur van 14 jaar was het noodzakelijk om bij 50% van de AHA-patiënten de klepprothese te vervangen wegens prothese-gerelateerde complicaties zoals PPM. Deze mate van klepgerelateerde complicaties is hoger dan beschreven in studies over patiënten met tricuspidaalklepprothese wegens een verworven hartafwijking met slechts een korte follow-up (gemiddeld 6-9 jaar) waarbij 10-35% een klepgerelateerde complicatie krijgt [14-18]. Het hoge aantal complicaties in onze populatie kan verklaard worden door de langere follow-up duur, maar ook door de jonge leeftijd van onze patiënten. Jonge patiënten zijn mogelijk minder trouw aan hun anticoagulantia wegens levensfase en levensstijl. Bovendien hebben jonge (vruchtbare) patiënten met een mechanische hartklep een verhoogd risico op kleptrombose gedurende de zwangerschap ondanks het strikt volgen van een antistollingsschema met vitamine-K antagonisten of heparine [19]. Jonge patiënten met een bioprothese lopen echter het risico op vroege achteruitgang (slijtage) van de klep [20,21]. Uit onze gegevens blijkt dat trombose in mechanische kleppen en slijtage van bioprothesen de meest voorkomende indicaties zijn voor heroperatie in volwassenen met AHA. Dit is vergelijkbaar met gegevens uit de literatuur [14,15,22-14]. Bovendien zien wij dat PPM het complicatie-vrije interval na een tricuspidalisklepvervanging significant beperkt. Wij benadrukken dat de keuze van het soort en maat klepprothese geindividualiseerd moet zijn en dat men altijd op de hoede moet zijn voor PPM.

Hoofdstuk 5

Long-term mitral valve prosthesis-related complications in congenital heart disease.

In kinderen met AHA wordt een slecht functionerende mitralisklep bij voorkeur gerepareerd, maar soms is vervanging van de klep onvermijdelijk. Kinderen met een mitralisklepprothese krijgen echter snel te maken met klepgerelateerde complicaties zoals slijtage van de bioprothese of PPM omdat het kind 'uit de klep groeit'. Dit leidt tot een hoog aantal heroperaties (13-37%) [25-31]. Mogelijke variabelen die voorspellen dat een prothese maar kort meegaat zijn jonge leeftijd [25] en kleinere prothese [25,28] ten tijde van implantatie en meerdere linkszijdige obstructieve hartafwijkingen bij de geboorte [32]. Of deze voorspellers ook van toepassing zijn op volwassen patiënten met AHA is nog onbekend. In hoofdstuk 4 beschrijven wij daarom de prothese-gerelateerde complicaties in 91 volwassen AHA-patiënten met een mitralisklepprothese die tussen 1978 en 2010 geimplanteerd is. De mediane leeftijd ten tijde van implantatie was 19 jaar (interkwartiele spreiding 13-44). Gedurende een mediane follow-up van 12 jaar kreeg bijna 50% van de patiënten te maken met een prothese-gerelateerde complicatie zodat in één-derde een heroperatie onvermijdelijk was. De meeste complicaties (75%) ontstonden toen de patiënten volwassen waren. Meestal was obstructie (PPM of pannus) de reden om de prothese te vervangen, gevolgd door biologische klepverslechtering, endocarditis en paravalvulaire lekkage. De aanwezigheid van linkszijdige obstructieve hartafwijkingen bij de geboorte, een kleine geïndexeerde klepmaat en een mitralisklepimplantatie vóór het jaar 2000 zijn onafhankelijke variabelen die gerelateerd zijn aan prothese-gerelateerde complicaties na een mitralisklepvervanging. Dit is deels te verklaren door het feit dat patiënten die de prothese pre-2000 kregen jonger waren wat de kans op een heroperatie vergroot. Daarnaast kregen patiënten met linkszijdige obstructieve AHA (mitralisklepstenose, (sub)valvulaire aortaklepstenose, of coarctatio aortae) kleinere mitralisklepprothesen. Mogelijk hebben patiënten met linkszijdige obstructieve hartafwijkingen kleinere hartafmetingen ten op zichte van hun lichaam hebben. De relatief kleine klepprothese vergroot de kans op PPM wat wij ook terugzien in onze studie: PPM komt vier keer zo vaak voor bij patiënten met linkszijdige obstructieve hartafwijkingen. Maar mogelijk zijn er nog andere risicofactoren die specifiek zijn voor patiënten met linkszijdige obstructieve hartafwijkingen die nog onbekend zijn.

Hoofdstuk 6

Pulmonary valve replacement: Long-term outcome of mechanical valve prostheses.

Bij veel patiënten met rechtszijdige AHA moet een slecht functionerende pulmonalisklep vervangen worden [33,44]. Bioprothesen hebben de voorkeur omdat zij een laag trombo-embolisch risico met zich mee brengen en omdat zij langzamer slijten dan linkszijdige bioprothesen, maar op de lange termijn moeten ook rechtszijdige bioprothesen vervangen worden wegens achteruitgang. Als alternatief kunnen mechanische pulmonaliskleppen geimplanteerd worden omdat zij duurzamer zijn. Een aantal studies met een relatief korte follow-up duur laat zien dat mechanische prothesen gebruikt kunnen worden op de pulmonalispositie, mits aan een strikt antistollingsbeleid wordt voldaan [35,36]. Of mechanische prothesen op de pulmonalispositie ook op de lange termijn goed functioneren is onbekend.

In hoofdstuk 6 beschrijven wij daarom de lange termijn follow-up van 66 AHA-patiënten met mechanische klepprothesen in de pulmonalispositie. De prothesen werden tussen 1987 en 2013 geimplanteerd op een gemiddelde leeftijd van 35 ± 13 jaar. Veelal was tetralogie van Fallot de onderliggende aandoening (77%). In totaal kregen 8 patiënten (12%) prothese-gerelateerde complicaties gedurende een gemiddelde follow-up van 6 ± 5 jaar waarvan kleptrombose de meest voorkomende was. Kleptrombose kwam in de meeste gevallen voor bij zwangere patiënten of bij patiënten die geen goed antistollingsbeleid volgden. Zes (9%) heroperaties waren nodig wat vergelijkbaar is met de percentages gerapporteerd bij bioprothesen [37,38]. De relatieve hoge mortaliteit (18%) wordt mogelijk verklaard door negatieve selectiebias omdat patiënten met ernstige AHA eerder een mechanische prothese kregen om toekomstige heroperatie wegens slijtage van een bioprothese te vermijden.

Het lange termijn succes van mechanische pulmonalisklepprothesen is beperkt wegens stollings- en bloedingscomplicaties. Het succes van mechanische pulmonaliskleppen kan mogelijk verbeteren door de patiënten met een laag trombo-embolisch risico te selecteren en door een strikt antistollingsbeleid.

Hoofdstuk 7

Aortic prosthesis-patient mismatch and diminished exercise capacity in adult patients with congenital heart disease.

Patiënten met linkszijdige AHA hebben soms een aortaklepvervanging nodig tijdens hun kindertijd. Vanwege het risico op late prothese-gerelateerde complicaties blijven deze patiënten vervolgens levenslang onder controle bij een cardioloog. PPM is een van deze complicaties die vaak ontstaat als het kind opgroeit en daardoor te groot wordt voor de prothese. De prevalentie van aortaklep PPM bij volwassenen met AHA is echter onbekend.

In de PROSTAVA database identificeerden wij 207 volwassen patiënten met een AHA en een aortaklepprothese die tussen 1973 en 2011 geimplanteerd is. De mediane leeftijd ten tijde van implantatie was 45 jaar (interkwartiele spreiding 35-53). De meeste patiënten (71%) hadden een mechanische klepprothese. Met behulp van echocardiografie bevestigden wij dat 19% van onze patiënten PPM heeft en nog eens 23% ernstige PPM. De prevelentie van (ernstige) PPM is hoger in patiënten met een mechanische klepprothese en in patiënten die jonger dan 18 jaar waren toen zij hun prothese kregen. In vergelijking met literatuur over patiënten met een aortaklepprothese wegens een verworven hartziekten is de prevalentie van ernstige PPM twee keer zo hoog in volwassenen met AHA [39,40]. In onze populatie hadden patiënten met PPM een significant slechter inspanningsvermogen. Zelfs na correctie voor TAPSE, log-getransformeerde NT-proBNP en chronotrope incompetentie blijft PPM significant gerelateerd aan een slechter inspanningsvermogen.

In dit hoofdstuk beschrijven wij dat PPM een veel voorkomend probleem is in volwassenen met AHA en een aortaklepprothese. Tevens moet PPM erkend worden in de kliniek en waar mogelijk vroeg vermeden worden omdat het een negatief effect heeft op de functionele capaciteiten van de patiënt.

Conclusie

Patiënten met AHA en cardiovasculaire prothesen verschillen op vele manieren van patiënten met verworven hartafwijkingen, maar wetenschappelijk bewijs voor de implicaties van deze verschillen is schaars. In dit proefschrift worden de lange termijn effecten van cardiovasculaire prothesen in AHA-patiënten beschreven. Tevens worden de eigenschappen van de prothese gerelateerd aan inspanningsvermogen in een unieke

en grote groep volwassenen met AHA. Onze resultaten hebben mogelijk invloed op de keuze van de prothese, de follow-up, de indicaties voor meer uitgebreide chirurgie (bijv. annulusplastiek), de indicatie voor heroperaties in patiënten met PPM en op de manier dat wij naar volwassen patiënten met AHA kijken.

Toekomstperspectieven

Volwassenen met AHA vertegenwoordigen een nieuwe patiëntenpopulatie waarvan we nog weinig weten. Onderzoek naar geïmplanteerde cardiovasculaire prothesen in deze patiënten is een van de aandachtsgebieden waarbij basale kennis zoals 'normale' hartafmetingen bij patiënten met AHA onmisbaar is. Tevens zal men zich richten op de functionele capaciteiten van deze patiëntenpopulatie. Vanwege alle complicaties die bekend zijn bij cardiovasculaire prothesen moeten we wellicht weg bewegen van slechts het turven van complicaties en juist nieuwe prothesen gaan ontwerpen die superieur presteren. Het gebruik van 'stentless' bioprothesen lijkt al een kleine stap voorwaarts, maar wellicht ligt de toekomst bij de ontwikkeling van gekweekte prothesen uit stamcellen van de patiënt zelf. Deze 'tissue-engineered' prothesen lijken op de eigenlijke structuur en kunnen wellicht meegroeien of zichzelf repareren [41]. Mogelijk kunnen cellen van een embryo met een AHA uit de navelstreng geoogst worden welke dan tot een volledig werkzame klep of buisprothese kunnen uitgroeien in een laboratorium. Deze kan dan geïmplanteerd worden zodra het kind geboren is.
Op dit moment zitten we nog in een ontdekkingsfase en worden gekweekte hartkleppen alleen nog maar bij dieren geïmplanteerd [42], maar de toekomst kan ons nog veel brengen.

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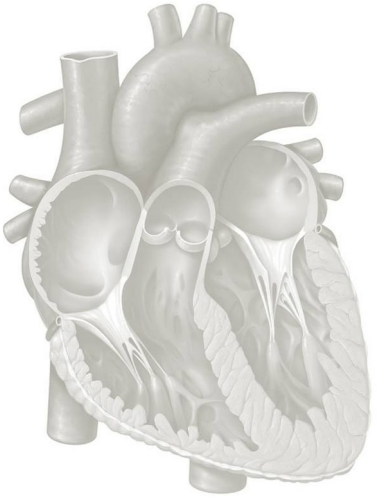
Dankwoord

Acknowledgements



"In de toekomst moge het niet meer nodig zijn de rol der vrouw apart te belichten, omdat dat dan eindelijk het geslacht bij de prestatie onbelangrijk wordt geacht. Bovenal won de vrouw door zelf de verantwoordelijkheid voor de dingen te durven gaan dragen en zodoende niet meer de man te blijven te beschouwen als een instrument dat men listig hanteren moet alvorens zijn zin te kunnen krijgen. De jaren die achter ons liggen mogen wenselijk bijdragen tot wederzijds begrip tussen de beide geslachten en ook tussen de verschillende generaties."

Openingstoespraak Nationale Vrouwententoonstelling 1898-1948.
H.K.H. Juliana van Oranje-Nassau, destijds koningin der Nederlanden (1948)

Als je gedurende 4 jaar met een 50% aanstelling een full-time project probeert te voltooien komt daar de nodige stress bij kijken. Gelukkig ben ik door de steun van vele collega's, vrienden en familie niet helemaal gek geworden en ben ik trots op het resultaat dat nu voor u ligt. Een aantal personen wil ik in het bijzonder bedanken.

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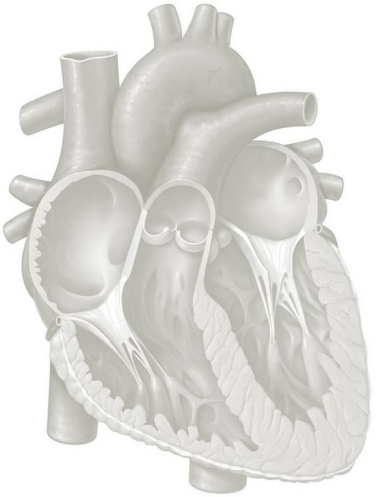
We're same same but different.

About the Author



"I always feel that the young doctors are only too anxious to experiment. After they've whipped out all your teeth, and administered quantities of very peculiar glands, and removed bits of our insides, they then confess that nothing can be done for us (generally because there's very little of the original 'us' left). I really prefer the old-fashioned remedy of big black bottles of medicine. After all, one can always pour those down the sink."

Miss Marple in "A Murder is Announced" by Agatha Christie (1890-1976)
Adapted by Alan F. Plater (1935-2010) for a screenplay in 1987

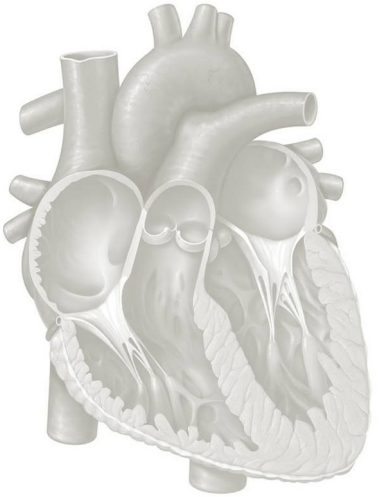
Ymkje Johanna van Slooten was born in the Netherlands on October 30th 1984 in Rockanje as the third daughter of Dirk Anne van Slooten and Maria Wilhelmina van Slooten-Postel. Shortly after her little brother was born, the family moved to Singapore where Ymkje attended the Dutch primary school "The Hollandse School" for almost 2 years. Back in Rockanje she finished her primary school (OBS de Hoeksteen) in 1996 and completed the first grade of secondary school at the Helinium in Hellevoetsluis in 1997. That same year the whole family moved to the United Kingdom where Ymkje enjoyed a bilingual education at Reed's School and the Rijnlands Lyceum in Cobham (Surrey). In 2002 she graduated with 4 A-levels and 2 AS-levels and moved back to the Netherlands where she enrolled at the Rijksuniversiteit Groningen as a medical student.

In 2007 she completed her Master research project at the Department of Cardiothoracic Surgery of the University Medical Center Groningen (UMCG) and presented her work at (inter)national congresses including the 5th World Congress of Pediatric Cardiology and Cardiac Surgery in Cairns, Australia. After a year of internships at the Medical Center Leeuwarden she returned to the UMCG and graduated as a Medical Doctor in July 2010.

In Groningen field hockey was one of her main interests, not only as a player but also as an umpire. During and after her medical studies she was trained as a national umpire and is now performing at the highest level in the Dutch field hockey league and persuing an international career.

Intrigued by the field of cardiothoracic surgery she started working at the Department of Cardiothoracic Surgery as a junior doctor following her graduation. In addition she worked at the Department of Cardiology as a PhD candidate on the PROSTAVA-project on which most of this thesis is based. To prepare for a degree in general medicine she left the Department of Cardiothoracic Surgery in September 2013 and started working at the Clinical Training Center (Klinisch Training Centrum) in Groningen as a teacher providing clinical education for fourth-year medical students. She has started her General Practitioner (huisarts) training programme in September 2014.

List of publications



"It has been a disastrous half. His work has been far from satisfactory. His prepared stuff has been badly learnt, and several of his test pieces have been torn over; one of such pieces of prepared work scored 2 marks out of a possible 50. His other work has been equally bad and several times he has been in trouble because he will not listen, but will insist on doing his work in his own way. I believe he has ideas about becoming a Scientist; on his present showing this is quite ridiculous, if he can't learn simple Biological facts he would have no chance of doing the work of a Specialist, and it would be sheer waste of time, both on his part, and of those who have to teach him."

John Gurdon's 1949 schoolmaster's report (1933 -)
Winner of the 2012 Nobel Prize of Physiology or Medicine

1. **van Slooten YJ**, Elzenga NJ, Waterbolk TW, van Melle JP, Berger RMF, Ebels T.
   The effect of additional cavopulmonary blood flow on timing of the total cavopulmonary connection.
   Ann Thorac Surg. 2012;93:2028-33.

2. Ebels T, **van Slooten YJ**, Elzenga NJ, Waterbolk TW, Berger RMF.
   Quantification of ventricular volume load in the context of a bidirectional cavopulmonary shunt: a theoretical treatise.
   Ann Thorac Surg. 2012;93:2022-7.

3. Freling HG, **van Slooten YJ**, van Melle JP, Mulder BJM, van Dijk APJ, Hillege HL, Post MC, Sieswerda GT, Jongbloed MRM, Willems TP, Pieper PG; PROSTAVA investigators.
   Prosthetic valves in adult patients with congenital heart disease: Rationale and design of the Dutch PROSTAVA study.
   Neth Heart J. 2012;20:419-24.

4. **van Slooten YJ**, Freling HG, van Melle JP, Mulder BJM, Jongbloed MRM, Ebels T, Voors AA, Pieper PG.
   Long-term tricuspid valve prosthesis-related complications in patients with congenital heart disease.
   Eur J Cardiothorac Surg 2014;45:83-9.

5. **van Slooten YJ**, van Melle JP, Freling HG, Bouma BJ, van Dijk APJ, Jongbloed MRM, Post MC, Leenders PM, Ebels T, Voors AA, Pieper PG.
   Long-term mitral valve prosthesis-related complications in congenital heart disease.
   Submitted

6. Freling HG, **van Slooten YJ**, van Melle JP, Ebels T, Hoendermis ES, Berger RMF, Hillege HL, Waterbolk TW, van Veldhuisen DJ, Willems TP, Pieper PG.
   Pulmonary valve replacement: Long-term outcome of mechanical valve prostheses.
   Submitted

7. **van Slooten YJ**, van Melle JP, Freling HG, Bouma BJ, van Dijk APJ, Jongbloed MRM, Post MC, Sieswerda GT, Huis in 't Veld AE, Ebels T, Voors AA, Pieper PG.
   Aortic prosthesis-patient mismatch and diminished exercise capacity in adult patients with congenital heart disease.
   Submitted

8. Freling HG, Willems TP, van Melle JP, **van Slooten YJ**, Bartelds B, Berger RMF, van Veldhuisen DJ, Pieper PG.
   Effect of right ventricular outflow tract obstruction on right ventricular volumes and exercise capacity in patients with repaired Tetralogy of Fallot.
   Am J Cardiol. 2014;113:719-23.

9. Wolff D, van Melle JP, Ebels T, Hillege H, **van Slooten YJ**, Berger RMF.
   Trends in mortality (1975-2011) after one- and two-stage Fontan surgery, including bidirectional Glenn through Fontan completion.
   Eur J Cardiothorac Surg. 2014;45:602-9